

REMARKS

Claims 1-28 and 34-43 are currently pending in the application. Claim 10 has been amended to correct a mistake in the previous response, when Applicants inadvertently amended it. Claim 10 as it stands now is the same as it was originally filed. Claims 1, 16, 34, 36 have been amended. Support for the amendment is found throughout the specification, for example, on page 6, lines 7-13. Applicants respectfully assert that no new matter has been added and request reconsideration of the claims currently pending in the application.

Rejection under 35 U.S.C. § 112

Claim 10 has been amended to return it to the scope as originally filed. The Examiner's note on page 2 of the advisory action concerning claim 10 is no longer applicable. The rejection has been obviated. Reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 103

On page 2 of the Office Action, claims 1-28 and 34-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ogle, et al. (U.S. Patent No. 5,958,669) in view of Yang, et al. (U.S. Patent No. 5,935,168). Applicants respectfully traverse the rejection.

Ogle, et al. discloses a method and apparatus for crosslinking a tissue using a semi-permeable membrane for screening out crosslinking compounds or oligomers not having the desired molecular weight or size. See col. 1 line 47 to col. 2 line 57. As noted by the Examiner, the tissue can be fixed by crosslinking with crosslinking agents

like glutaraldehyde. The crosslinking compounds, such as dialdehydes, can polymerize spontaneously in solution, generating oligomers of varying sizes or molecular weights. See col. 4, lines 1-9. By the screening method described, the oligomers having the correct molecular weight can pass through the screen to crosslink the tissue. See col. 5, lines 22-36.

Yang, et al. discloses a tissue already crosslinked with glutaraldehyde to form a fixed tissue, as in Ogle et al. See col. 3, lines 2-5. This crosslinked tissue is then reacted with a diamine to replace at least some of the carboxyl groups present on the collagen and/or elastin molecules with non-carboxyl side groups. This replacement of the carboxyl groups does not affect the glutaraldehyde crosslinked portion. See col. 3, lines 2-17, and Figure 2. This is done because glutaraldehyde fixed tissue which contains collagen and/or elastin is prone to calcification. See col. 3, lines 2-11, and 44-64. Applicants respectfully submit that there is no bonding of the crosslinkers, such as glutaraldehyde, to bridge molecules, as the glutaraldehyde crosslinkers are already crosslinked to the tissue via the aldehyde functional groups. See Figure 2. This follows what is also taught in Ogle, et al. In addition, while Ogle, et al. screen out all glutaraldehyde molecules not having the correct size to span the gap between the tissues to be crosslinked, the rinsing action in Yang, et al. removes residual glutaraldehyde from the tissue after fixing the tissue with glutaraldehyde. See Ogle, et al. col. 1, line 47 to col. 2, line 57; and Yang, et al. col. 5, lines 40-50.

On the other hand, claims 1 and 16 disclose a tissue comprising a linker having one end bonded to the tissue and the other end to one end of a bridge molecule, while the other end of that same bridge molecule is bonded to one end of another linker

molecule. Thus, a bridge molecule is bonded to two or more linkers. A linker links to the tissue on one end, and instead of linking to a different portion of the tissue on its other end, as taught in Ogle, et al. and Yang, et. al., it is instead linked to a bridge molecule that is distinguished chemically from the linker. In addition, unlike linkers, bridges are generally non-reactive with other bridges. See page 6, lines 7-13.

While it is true that both Ogle, et al. and Yang, et al. teach the use of glutaraldehyde as a crosslinker, neither teach a tissue having glutaraldehyde linkers and bridge molecules that are chemically different from glutaraldehyde, that bond at least two of such linkers together. As noted, Ogle, et al. is concerned with a crosslinker having the correct size, such as glutaraldehyde or its polymerized oligomer, for such linking action, and the deficiency is not supplied by Yang, et al., as Yang, et al. also teaches the same crosslinked tissue linked by glutaraldehyde. See Figure 2. No bridge molecule, chemically different from the crosslinker, and generally non-reactive with other bridges is mentioned or taught in Yang, et al. Therefore, the combined teaching of Ogle, et al. and Yang, et al. do not teach nor suggest how to arrive at the subject matter of claims 1 and 16, and claims 1 and 16 are not obvious over Ogle, et al. in view of Yang, et al.

Claims 34 and 36 disclose bridge molecules bonded to two or more modified sites of the tissue, and the bridges are generally non-reactive with other bridges. This is also not taught in Ogle, et al. This deficiency is again not supplied by Yang, et al., as noted above. In addition, Yang, et al. teaches that glutaraldehyde can either be used to crosslink the tissue itself, or if amines are used to treat the tissue first to minimize calcification, glutaraldehyde can be used to crosslink the tissue after replacing some of

the carboxyl groups with diamines, again only teaching the use of linkers alone, and not the use of bridges to link linkers. See Figure 2. There is no bonding of bridge molecules to two or more modified sites, since no bridge molecules are disclosed or motivated. Therefore, bridge molecules for bonding modified sites of the tissue are not taught by the combined teaching of Ogle, et al. and Yang, et al.

With regard to claims 1, 16, 34 and 36, the Examiner suggests that after reacting with glutaraldehyde as disclosed in Ogle, et al., it would have been obvious to react with a diamine and then with additional glutaraldehyde as suggested by Yang, et al. to arrive at the claimed bridges. Applicants respectfully submit that this reasoning fails to recognize that in both Ogle, et al. and Yang, et al., one end of the glutaraldehyde molecule is linked to one part of the tissue and the other end to another part of the tissue, which in effect fixed the tissue with the crosslinker, leaving no free end of the crosslinker to be bonded to a bridge molecule. To cause one end of the crosslinker to be detached from tissue so that it can be bonded to a bridge molecule will require a different mechanism, and hence a different invention, which is not found in the teachings of Yang, et al.

In response to Applicants' arguments, the Examiner noted that since the present specification discloses that the linker and bridge molecule can be applied to the tissue sequentially, if both ends of glutaraldehyde react with tissue, then this embodiment will not work since the tissue is contacted with the glutaraldehyde in the absence of the bridge molecule, as in Ogle, et al. and Yang, et al. The fact that this embodiment works supports that some free aldehyde groups will remain after crosslinking with glutaraldehyde. Applicants respectfully submit that this point strengthens Applicants'

position that the present invention is distinguished from the cited references. To fix a tissue requires the presence of a crosslinker having the desired size to span the gap between the sites. Ogle, et al. screens for glutaraldehyde oligomers having the desired length to fix the tissue. Likewise, Yang, et al. fixes the tissue using glutaraldehyde of the required size. They both concentrate on having a linker large enough to accomplish the goal. At the same time, there is no teaching that there are free aldehyde groups remaining after crosslinking with glutaraldehyde as Yang, et al. rinse the tissue afterwards to remove residual glutaraldehyde. See col. 5, lines 40-50. On the other hand, the present inventors recognize that using linkers not having the desired length to span the gap between the tissue sites is not a disadvantage, and screening is not needed to make sure that such undersized linkers are removed, as taught in Ogle, et al., but rather, is an advantage. This advantage of having undersized linkers allows the use of a bridge molecule to connect the free ends of at least two such linkers, which gives more options, including the choice of bridge molecules for fixing tissues not contemplated by the cited references. If greater flexibility of the crosslinked tissue is desired, the bridge molecule chosen can include a saturated hydrocarbon backbone without any rings. See page 19, lines 5-7 of the specification. If a more rigid fixed tissue is desired, it can be accomplished by the addition of unsaturated bonds or rings to the bridge. See page 19, lines 8-10. This novel approach is not taught or suggested anywhere in the prior art.

Further, the Examiner suggests on page 4 of the final Office Action that in the final step in Yang, et al., the tissue is reacted with glutaraldehyde after reacting with a diamine, resulting in the diamine being the linker and the glutaraldehyde being the

bridge molecule which will have one end coupled to an amine of a diamine already bonded to the tissue and the other end coupled to an amine of another diamine that is bonded to the tissue at a different site. Applicants again respectfully traverse this point.

Glutaraldehyde is a known linker or modifier of tissues, as taught in both Ogle et al. and Yang, et al. Such linkers can polymerize spontaneously in solution, again as taught in Ogle, et al. Bridges, on the other hand, are not linkers and are chemically different from linkers, as taught in the present invention. Further, bridges are generally non-reactive with other bridges. There is no teaching or suggestion in either cited reference of how to modify glutaraldehyde so that it will not polymerize spontaneously. Therefore, the teaching of glutaraldehyde in the reference does not teach or motivate a bridge.

Finally, Applicants will address the remaining points of the Examiner's arguments in the Advisory Action below:

- a. On page 3 of the Advisory Action, the Examiner points out that where the linker can contain an aldehyde group and be glutaraldehyde, all glutaraldehyde will not contain both ends bound to tissue when crosslinking occurs in Ogle, et al. and Yang, et al., and when the diamine is added, there will be some free ends of the glutaraldehyde that will react with the amine groups of the diamine. Applicants submit that this is not the teaching of Ogle, et al. or Yang, et al. As discussed above, to fix a tissue requires the presence of a crosslinker having the desired size to span the gap between the sites. Ogle, et al. screens for glutaraldehyde oligomers having the desired length to fix the tissue. Likewise, Yang et al. fixes the tissue using

glutaraldehyde of the required size. They both concentrate on having a linker large enough to accomplish the goal. In fact, Yang et al. specifically teaches that after fixing the tissue with glutaraldehyde, it is rinsed to remove residual glutaraldehyde. See col. 5, lines 30-50. The addition of diamine is therefore not to react with free glutaraldehyde in a crosslinked tissue, but to replace at least some of the carboxyl groups present on the collagen and/or elastin molecules with non-carboxyl side groups, as already discussed above. Why else will Yang, et al. go on to teach that additional glutaraldehyde can be added for further treatment for additional crosslinking after diamines are used to replace carboxyl groups? See col. 6, lines 1-13.

- b. Both the teaching of pre-screening for the correct size of glutaraldehyde for use to span the gap between tissues to be crosslinked or the rinsing after crosslinking with glutaraldehyde to remove residual glutaraldehyde teaches away from the present invention where bridges are used to connect linkers. The crosslinked tissues of the cited art has one end of a glutaraldehyde crosslinker linked to a tissue and the other end linked to another tissue. No bridges are involved or contemplated in the cited art. In addition, with bridges, Applicants can fix tissue with more options in the choice of linker sizes, types, as well as producing fixed tissues with varying softness and rigidity. This is clearly not taught or motivated in the cited art.
- c. The Examiner contends, on page 4 of Advisory Action, that claims 34 and 36 encompass the embodiment in Fig. 2 of Yang, et al. where glutaraldehyde bridges free amine groups of diamines reacted with activated carboxyl groups

of tissue. The Examiner also states that claims 35 and 37 encompass first crosslinking tissue with glutaraldehyde and then reacting with a diamine as in Yang, et al. Applicants respectfully submits that glutaraldehyde is a not a bridge, but a linker. Claims 34-37 comprise bridges bonded to two or more modified sites in the tissue. This is neither taught nor motivated in Yang, et al. The diamines in Yang, et al. react with carboxyl groups to form modified sites, and glutaraldehyde is added to crosslink these sites. No bridge is contemplated.

- d. The Examiner's contention on page 5 of the Advisory Action that there is no teaching in the present specification how to modify glutaraldehyde so that it will not polymerize spontaneously is not to the point. Applicants set forth glutaraldehyde as a linker, and since a bridge is chemically different from a linker, glutaraldehyde, therefore, cannot be a bridge. Therefore, the Examiner's further contention that glutaraldehyde is a bridge and that neither Ogle, et al. nor Yang, et. al. refer to glutaraldehyde as a linker and that nothing in the prior art teaches that a linker function requires a crosslinking agent such as glutaraldehyde is also not to the point. See page 5, lines 17-20 of Applicant's specification. Applicants specifically disclose that linkers can be crosslinking agents, though linkers include more than crosslinking agents.

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the

prior art reference, or combination of references, must teach or suggest all the claim limitations. MPEP § 2142. Applicants respectfully submit that, Ogle et al. teach that glutaraldehyde crosslinkers with required size are used to crosslink tissue. No bridges are taught or motivated. Yang, et al. does not supply the deficiency of Ogle, et al., as no bridge molecules, generally non reactive with other bridges, and chemically different from linkers, or bridge molecules generally non reactive with other bridges, linking sites in tissues that have been modified, are suggested or taught by the combined teachings of Ogle, et al. and Yang, et al. The cited art fails to disclose all the claim limitations.

Dependent claims 2-15, 17-28, 35, and 37-43, which are dependent from their respective independent claims 1, 16, 34, and 36, were also rejected under 35 U.S.C. §103(a) as being unpatentable over Ogle, et al. (U.S. 5,958,669) in view of Yang, et al. (5,935,168).

While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 1, 16, 34 and 36. These dependent claims include all of the limitations of the base claims and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 2-15, 17-28, 35, and 37-43 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 1-28 and 34-43 under 35 U.S.C. § 103(a) as being unpatentable over Ogle, et al. in view of Yang, et al..

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' attorney of record, Hallie A. Finucane at (952) 253-4134.

Respectfully submitted,

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